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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,648	10/05/2000	Mark F. Charette	CIBT-P01-569	7787

28120 7590 07/25/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/509,648	CHARETTE ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-8,16-18,35,37 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *39-41* is/are allowed.

6)☒ Claim(s) *2,5-8,16-18,35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 2, 5, 6, 35, and 39-41 have been amended as requested in the amendment filed on May 1, 2007. Claims 1, 3-4, 9-15, 19-34, 36 and 38 were canceled by Applicant in previous amendments.

Following the amendment, claims **2, 5-8, 16-18, 35, 37**, and **39-41** are pending and under examination in the current office action. The claims are examined to the extent of the following elected species: Alzheimer's disease from the disorder group, cytokine antagonist from the agent capable of releasing morphogen activity group, (2-p-bromocynnamylaminoethyl)-5-isoquinolinesulfonamide from the protein kinase A inhibitor group, SEQ ID NO: 2 from the morphogen amino acid sequence group, OP-1 from the morphogen group, and retinoid receptor from the molecule that binds an endogenous ligand group.

Withdrawn Objections and Claim Rejections

The objection to claim 5 as being of improper dependent form for failing to further limit the subject matter of a previous claim, set forth at p. 4 of the previous office action (11/13/2006), is withdrawn in view of Applicants' arguments and amendments to the claims.

The rejection of claims 5-6, 39 and 40 under 35 U.S.C. 112, second paragraph, as set forth at pp. 11-12 of the previous office action mailed November 13, 2006, is withdrawn in view of Applicants' amendments to the claims.

The rejection of claims 39-41 under 35 U.S.C. 112, first paragraph, as set forth at pp. 4-11 of the previous office action (11/13/2006), is withdrawn in view of Applicants' arguments at p. 7, second paragraph, of the response filed May 1, 2007 and in view of Applicants' amendments to the claims.

Maintained Objections and Claim Rejections

The objection to claims 2, 8 and 16-17, as noted at p. 4 of the 03/23/2006 office action and at pp. 3-4 of the previous office action (11/13/2006), regarding the issue that the claims are not limited to the elected species, is maintained and held in abeyance until allowable subject matter is identified.

Claim Rejections - 35 USC § 112, 1st Paragraph

The rejection of claims 2, 5-8,16-18, 35 and 37 under 35 U.S.C. 112, first paragraph (scope), is maintained for reasons of record. The specification, while being enabling for a method of reducing leukemia inhibitory factor (LIF)-induced dendritic retraction comprising adding an antibody against gp130 to neurons *in vitro* that have been treated with LIF and osteogenic protein-1 (OP-1) and wherein said antibody

reduces LIF-induced dendritic retraction, *does not* reasonably provide enablement for a method for promoting neuronal cell dendritic growth as broadly claimed either *in vitro* or *in vivo*. Additionally, the specification is enabling for a method of reducing ciliary neurotrophic factor (CNTF)-induced dendritic retraction comprising adding phosphatidylinositol-specific phospholipase C (PI-PLC) to neurons *in vitro* before the neurons have been treated with CNTF and OP-1 and wherein said PI-PLC reduces CNTF-induced dendritic retraction. The specification is also enabling for a method of reducing dendritic retraction in a neuron *in vitro* in the presence of a morphogen or OP-1 and a gp130 protein comprising contacting the neuron with a composition comprising a monoclonal antibody to a gp130 protein, thereby reducing dendritic retraction *in vitro*. Finally, the specification is enabling for a method of reducing the inhibitory effects of LIF on OP-1 stimulated dendritic growth comprising adding an anti-LIF antibody to neurons *in vitro* that have been treated with LIF and OP-1 and wherein said antibody reduces the inhibition of LIF on OP-1 stimulated dendritic growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the response filed May 1, 2007, Applicants present the following arguments: 1) with respect to the *in vivo* use of the components of the composition recited in the instant claims, Applicants argue that such compositions have been used *in vivo* in experimental animals, albeit for purposes other than reducing the inhibition of morphogen induced dendrite growth, and therefore it would have been within the knowledge of one skilled in the art to practice the method to promote dendritic growth.

2) The *in vitro* systems used by Applicants reflect *in vivo* utility of a composition, because post-filing art supports the utility of morphogens *in vivo*, such as to improve damages to neurons due to stroke (such as Chang et al. *Stroke*, 2003; 34: 558-564; cited by Applicants). Thus, Applicants assert that enhancing morphogen activity to elicit neuronal dendritic growth is reasonably expected to be similar to increasing morphogen activity by administering a morphogen itself. 3) With respect to the statement that cells injured by neurodegenerative diseases are dead or dying, Applicants argue that in the broadest sense, any non-immortalized and/or non-stem cell can be said to be dying at any given time, and an injured cell may still be repaired. And, 4) with respect to cell types, Applicants assert that the effect of morphogens is not limited to sympathetic neurons, and cite Chen & Panchision (*Stem Cells*, 2007; 25:63-68) for support.

Applicants' arguments as they pertain to the rejection have been fully considered but are not found to be persuasive.

With respect to Applicants' first argument, the fact that compositions such as cyclic AMP antagonists have been used experimentally in animals is noted but not persuasive because, as Applicants note, such agents were administered for purposes other than those instantly claimed. Agents such as cyclic AMP antagonists and anti-gp130 protein antibodies, for instance, can elicit any number of effects *in vivo* – both known and unknown, generic and specific – and many of these effects having nothing to do with neuronal cell dendritic growth. For example, gp130 is a common signal transducing component of the functional receptor complexes for the interleukin (IL)-6 family of cytokines, ie, IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M, ciliary

neurotrophic factor, and cardiotrophin-1. These cytokines exhibit pleiotropic biological activities in, for instance, immune, hematopoietic, and neural systems, and function in a redundant manner owing to the shared usage of gp130. The actions of cAMP are even more fundamental and thus shared by numerous cellular and molecular signaling pathways. Thus, administration of a cAMP antagonist or a gp130 antibody alone to an animal would have far-ranging, potentially undesirable, and therefore unpredictable effects depending on how much, when and in what manner the agent is administered. Accordingly, even though the administration of the claimed agents to animals may have been known to one of skill in the art at the time the invention was filed, such demonstration is not commensurate in scope with the current invention and therefore does not provide adequate support for a method of promoting neuronal cell dendritic growth *in vivo* encompassed by the instant claims.

With respect to Applicants' second argument, while the amended claims do narrow the scope of the claimed invention to dendritic growth, the claims still read upon *in vivo* methods. In particular, the broadest reasonable interpretation of claim 8, as derived from claim 2 for example, encompasses treatment of such neurodegenerative disorders as Alzheimer's disease, Parkinson's disease, Huntington's disease, and dementia, among others, which have proven to be recalcitrant to treatment in the art (see references listed on p. 13, section (v) of the 07/24/2004 office action). Regardless, the Examiner does not contest the utility of an administered morphogen to elicit therapeutic effects, as is noted by Applicants in post-filing art and in US patents 6,723,698 and 6,506,729. However, the instant claims are drawn to contacting a

neuron with an agent that promotes morphogen activity by inhibiting an antagonist of morphogen activity. Thus, the currently claimed method is part of a mechanism for promoting neuronal cell dendritic growth that is one or more steps removed from simply administering a morphogen itself to the animal or neuron. For reasons stated previously and above regarding the unpredictability of extrapolating *in vitro* results to *in vivo* effectiveness, enhancing morphogen activity using an antagonist of a morphogen antagonist would, therefore, not reasonably be expected to be similar to administration of a morphogen itself.

With respect to Applicants' third argument regarding cells injured by neurodegenerative diseases, the Examiner notes that it is true that injured cells may be repaired, however, in cases such as neurodegenerative disease, for example, much of the pathology is characterized by necrotic and/or apoptotic neurons beyond hope of repair. However, irrespective of the particular status of the cell – injured, dying or dead – the main point is that the treatment of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's and stroke, etc. (all of which would comprise injured neurons) is extraordinarily unpredictable, particularly when extrapolating laboratory data to clinical efficacy. The complex cellular milieu that neurons are subjected to at the time of injury is difficult to replicate *in vitro*, as there may be multiple factors present at the site of injury contributing directly or indirectly to the inhibition of morphogen activity. For example, the presence of non-neuronal cells can influence distinct behaviors in either peripheral or central neurons, such that *in vitro* culturing conditions are not predictive of the *in vivo* environment to which neurons are exposed

during injury. Thus the skilled artisan would encounter undue experimentation due to great unpredictability when converting the results of tightly controlled *in vitro* findings using cultured cells into effective *in vivo* therapeutic methods, particularly with respect to neurons injured by a neurodegenerative disease or stoke. Also, it was well known in the art at the time of the invention that not all differentiated cell populations are equally capable of renewal in an organism. See, for example, US 5,652,118 (Ozkaynak et al.), who state,

> The degree of morphogenesis in adult tissue varies among different tissues and is related, among other things, to the degree of cell turnover in a given tissue. On this basis, tissues can be divided into three broad categories: (1) tissues with static cell populations such as nerve and skeletal muscle where there is no cell division and most of the cells formed during early development persist throughout adult life; (2) tissues containing conditionally renewing populations such as liver where there is generally little cell division but, in response to an appropriate stimulus, cells can divide to produce daughters of the same differentially defined type; and (3) tissues with permanently renewing populations including blood, testes and stratified squamous epithelia which are characterized by rapid and continuous cell turnover in the adult. Here, the terminally differentiated cells have a relatively short life span and are replaced through proliferation of a distinct subpopulation of cells, known as stem or progenitor cells (col. 1).

Finally, claims 2, 5, 8, 35 and 37 recite culture conditions incapable of achieving the desired result, namely, dendritic growth in neurons. The claims are drawn to methods comprising contacting a neuron with a composition comprising a component, wherein the component is selected from: a monoclonal antibody to a gp130 protein, phosphatidylinositol-specific phospholipase C (PI-PLC), (2-p-bromocynnamylaminoethyl)-5-isoquinolinesulfonamide (H-89), and enantiomers of

cAMP or dibutyryl cAMP. As written, the exposure of one of these components alone to sympathetic neurons would not induce dendritic growth nor reduce dendritic retraction, as evidenced by Figures 5, 9 and Table III on p. 33 of the instant application. These components are shown only to reduce the effects of exogenously applied neuropoietic cytokines, such as CNTF or LIF, and do not affect dendritic outgrowth either when applied to cultured neurons alone or in combination with a morphogen such as OP-1. Additionally, the agent PI-PLC was shown only to antagonize CNTF-specific inhibition of OP-1, and was incapable of affecting LIF-mediated OP-1 inhibition (see Figure 9). A method requiring PI-PLC would thus be further limited in scope than a method requiring a monoclonal antibody to a gp130 protein, for instance. Because the claims as written do not require a neuropoietic cytokine such as CNTF or LIF to be present in the culture conditions, and the skilled artisan would not expect these or other neuropoietic cytokines to be present in uninjured or unstimulated pure neuronal cultures, undue experimentation would be required to practice the methods of claim 2 and claims dependent therefrom. For example, the recited methods would require a determination of what exactly is inhibiting the morphogen prior to being able to determine which component would be best suited to overcome this inhibition, because, as previously indicated, not all components will antagonize all morphogen inhibitors.

Moreover, as stated previously, the specification provides no guidance or support demonstrating the use of protein kinase A inhibitors, such as H-89 and sterically constrained enantiomers of cAMP and dibutyryl cAMP, to reduce the cAMP-induced inhibition of dendritic growth-promoting effects of morphogens such as OP-1. The

instant specification only demonstrates that agents that increase cAMP levels, such as forskolin and dibutyryl cAMP, were capable of reducing OP-1-mediated dendritic growth in a dose-dependent manner. However, there is no indication that the converse would be true, that is, that cAMP inhibitors (or PKA inhibitors, which would interfere with cAMP signaling) would enhance OP-1 dendritic growth. Further, Applicant provides no guidance as to the ability of PKA inhibitors to antagonize CNTF or LIF, which neuropoietic cytokines are responsible for inhibiting OP-1-mediated dendritic growth. As written, the exposure of one of these components alone to neurons would not be expected to induce dendritic growth nor reduce dendritic retraction, as evidenced by Chijiwa et al. (*J Biol Chem.* 1990; 265(9): 5267-5272). Chijiwa et al. demonstrate that addition of the protein kinase A inhibitor H-89 to neuronal cultures comprising either forskolin or NGF had no effect on neurite outgrowth, and even *decreased* neurite outgrowth in forskolin-treated neurons (see Figure 4, p. 5269). The art thus recognizes that protein kinase A inhibitors are not sufficient on their own to facilitate growth-promoting effects to a neurons' morphology. Accordingly, one skilled in the art would not expect that such components would be capable of reducing inhibition of dendritic growth-promoting effects of endogenous morphogens, particularly if the inhibition is due to neuropoietic cytokines such as CNTF or LIF.

Finally, only Applicants' arguments and supporting evidence regarding the effects of morphogens not being limited to sympathetic neurons (as in the review by Chen & Panchision noted above) are found to be persuasive, and the enablement rejection has be modified accordingly. However, this only addresses one component of the

enablement of the instant methods, and thus for all of the reasons stated above the rejection of claims 2, 5-8,16-18, 35 and 37 is still maintained.

Therefore, due to the large quantity of experimentation necessary to practice *in vivo* methods and particular *in vitro* methods, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administering a molecule to a subject, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

Claims 2, 5-8,16-18, 35 and 37 are rejected. Claims 39-41 are subject to allowability.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
July 20, 2007

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646